Novel Preclinical Tools for Predictive ADME-Toxicology

RFA Number: RFA-RM-04-023

Part I - Overview Information

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH), (http://www.nih.gov/)

Components of Participating Organizations
This Request for Application (RFA) is developed as an NIH Roadmap Initiative (http://nihroadmap.nih.gov /). All NIH Institutes and Centers (ICs) participate in Roadmap initiatives. This RFA will be administered by the National Institutes of General Medical Sciences (NIGMS) (http://www.nigms.nih.gov/) on behalf of the NIH.

Announcement Type
New

Catalog of Federal Domestic Assistance Number(s)
93.859

Key Dates
Release Date: October 27, 2004
Letters Of Intent Receipt Date: December 17, 2004
Application Receipt Date: January 21, 2005
Peer Review Date: June or July 2005
Council Review Date: September 2005
Earliest Anticipated Start Date: September 10, 2005
Additional Information To Be Available Date (Url Activation Date):
Expiration Date: January 22, 2005

Executive Summary

The NIH invites grant applications to support the development, standardization, and validation of novel approaches to obtain comprehensive absorption, distribution, metabolism, excretion (ADME) and toxicological (TOX) profiles that could better predict how new molecular entities will perform in humans to reduce the failure rate in clinical testing. This is an NIH Roadmap initiative. This funding opportunity will use the R21 Exploratory/Developmental Research Grants award mechanism. This RFA solicits applications that explore novel, ?high-risk,? and ?high-impact? approaches to achieve this goal, rather than incremental technology development that is already supported by current NIH programs.

The NIH intends to commit approximately $2 million in FY 2005 to fund four to seven new grants in response to this RFA. An applicant may request a project period of up to four years and a budget for direct costs up to $250,000 per year. Individuals with the skills, knowledge, and resources necessary to carry out the proposed research are invited to work with their institution to develop an application for support. An individual may submit only one application as the principal investigator. Organizations which may apply include for-profit or non-profit groups, public or private institutions, state or local governments, and foreign or domestic organizations. Multi-disciplinary teams of investigators are particularly encouraged to respond to this RFA. Applications must be prepared using the PHS 398 form. Instructions and application forms may be obtained at http://grants.nih.gov/grants/funding/phs398/phs398.html.

Telecommunications for the hearing impaired: TTY 301-451-0088

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

The National Institutes of Health invite R21 Exploratory/Developmental Research Grant applications to support the development, standardization, and validation of novel approaches and modern preclinical tools for obtaining comprehensive ADME/TOX profiles that could better predict how new molecular entities will perform in humans to reduce the failure rate in clinical testing. This RFA has been developed for the Molecular Libraries and Imaging Initiative of the NIH Roadmap.

1. Research Objectives

Background

The completion of the Human Genome Project and recent advances in our understanding of the molecular mechanisms of diseases have provided increasing numbers of newly defined biological pathways and networks with potential preventive or therapeutic targets. The development of molecular diversity libraries and screening of these libraries have provided tremendous opportunities to discover new chemical and biological agents for the prevention and treatment of diseases. This created the belief that increasing numbers of new molecular entities would enter clinical testing and would receive approval from the Food and Drug Administration (FDA) to treat human disorders. However, this has not occurred. Many candidate agents are failing during clinical testing because of their unfavorable pharmacokinetic properties, unacceptable adverse effects, or major toxicities, as well as the lack of efficacy.

The safety of each new chemical entity must be demonstrated prior to its entry into clinical trials. Investigational New Drug (IND) applications to the FDA require chemistry, manufacturing, and control information and results from preclinical toxicology studies for the safety of new agents. Results of nonclinical pharmacokinetic studies for defining ADME properties, addressing important safety issues, or assisting the evaluation of toxicology data for investigational new agents are highly desirable in IND submissions.

Preclinical pharmacokinetic studies characterize and compare ADME in different species and often allow extrapolation to humans with recommendations for optimal route and schedule in early clinical trials. Toxicology studies are generally conducted in two animal species (one rodent species, either mice or rats, and one non-rodent species such as dogs or monkeys) to estimate the safe starting dose in clinical studies, maximum tolerated dose, dose-dependent toxicity, reversibility of adverse effects, and organ toxicities to be monitored in clinical studies. These animal studies are expensive, time-consuming, and have limitations in reliably predicting potential safety problems in humans, in understanding molecular mechanisms underlying ADME/TOX properties, and in evaluating large numbers of candidate agents screened from molecular diversity libraries. Undesirable ADME and toxicological characteristics of molecular entities are some of the leading causes of attrition during drug development. This RFA is intended to support the development, standardization, and validation of novel approaches for obtaining comprehensive ADME/TOX profiles that could better predict how chemical compounds will perform in humans to reduce the failure rate in clinical testing.

Partially due to polymorphisms of human genes encoding drug-metabolizing enzymes, drug transporters, drug targets, or other target-associated proteins, it has been challenging to predict pharmacokinetic properties of drug candidates in individual patients. Current toxicity prediction models or methods may fail to detect serious human safety problems associated with many new chemical agents. Occasionally, early studies in animal models provide data which suggest the possibility of safety problems that never materialize in humans, unnecessarily eliminating new molecular entities from further development. There is a significant need to develop standardized and validated tools for fast, economical, confident, and efficient prediction and determination of ADME/TOX properties of candidate agents early in preclinical studies in order to reduce the number of drug candidate failures at the most costly part of the process, clinical trials.

An NIH Summit Workshop on Predictive Drug Toxicology was held on June 15?17, 2004 to discuss needed scientific advancements and technologies to improve preclinical evaluation of chemical entities that will lead to a reduction in failures due to undesirable ADME/TOX properties (http://nihroadmap.nih.gov/molecularlibraries/WorkshopSummary-PredictiveToxicology-0604.pdf).

The FDA recently published a report entitled ?Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products? (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html). One of the purposes of this FDA initiative is to invite academic researchers, product developers, patient groups, and other stakeholders to join the FDA in facilitating the translation of recent gains in scientific knowledge and advanced bioinformatics and molecular analysis technologies into the creation of ?new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs.? One pharmaceutical company estimated ??that clinical failures based on liver toxicity alone have cost them more than $2 billion in the last decade ?? The FDA report also indicated that ? ? 10% improvement in the prediction of drug failures would lead to a $100 million saving in development costs per drug.?

Objectives and Scope

The objective of this RFA is to support Exploratory/Developmental research grants for the development, standardization, and/or validation of economical, improved tools for efficient, reliable prediction and determination of ADME/TOX characteristics of chemically diverse agents and drug-drug interactions in human. The applicants are invited to translate scientific advances in evaluating pharmacokinetics and toxicology of chemical compounds, and emerging, advanced strategies in bioinformatics, computational techniques, molecular and cellular assays, nanotechnology, and imaging technologies into the development of tools for confident preclinical evaluation of candidate agents. This RFA solicits applications that explore novel, ?high-risk,? and ?high-impact? approaches to achieve this goal, rather than incremental technology development that is already supported by current NIH programs. The applicants should also clearly address how their applications will provide new scientific advancements and technologies that are relevant to the preclinical evaluation of chemical compounds, and discuss their potential impacts on the detection of human toxicities that cannot already be accomplished with existing procedures. This RFA does not support pharmacology studies for the evaluation of drug efficacy.

Multi-disciplinary teams of investigators from different institutions are encouraged to respond to this RFA. T eams of scientists are encouraged to translate recent basic science discoveries into new tools for preclinical evaluation of new molecular entities. Teams may consist of basic biomedical scientists, chemists, engineers, statisticians, experts in bioinformatics, and scientists involved in pharmaceutical studies. International collaborations may be needed for the establishment of certain preclinical evaluation tools. Young investigators are encouraged to participate in the proposed collaborative, integrated research efforts. Collaborations between multiple investigators and organizations can be difficult because participating parties will have legitimate claims for intellectual property. Applicants are required to address intellectual property issues in advance as part of the application in order to prevent interference with the progress of research.

Examples of preclinical ADME/TOX evaluation tools include, but are not limited to:

- Clinically relevant samples including specimens from people with idiosyncratic and other adverse drug reactions;
- Statistical models developed from preclinical and available clinical data;
- Computational (in silico) models including data integration tools that link mRNA levels, protein expression levels, protein activities, and metabolite profiles (systems biology) with chemical scaffolds and ADME/TOX parameters;
- Quantitative structure-activity relationship (QSAR) models;
- ADME models for pediatric populations;
- Primary human or mammalian cells;
- Human or mammalian cells derived from stem cells;
- Tissue slices;
- Isolated organs;
- Immortalized human hepatocytes;
- Standardized and well-controlled tissue or cell cultures, co-cultures, humanized, multicellular cultures, and three-dimensional cultures that mimic human liver or other organs/tissues;
- Genetically modified animals or cells such as transgenics and knockouts of enzymes and transporters;
- Various non-mammalian organisms;
- Panels of recombinant human enzymes;
- Sub-cellular fractions;
- Genetic, genomic, proteomic, and metabolomic profiles;
- Multiplexed biomarker assays employing advanced technologies including microarrays, chips, beads, microfluidics, nanotechnology, and biosensors;
- In vitro and in vivo imaging technologies;
- Standardized analytical methods and quantitative in vitro assays.

Preclinical tools or models must be predictive of ADME/TOX characteristics in human, and may be validated for:

- Predicting intestinal absorption, membrane permeability, and bioavailability;
- Evaluating effective concentration of a bioactive compound (either a parent drug or its metabolite), and in vivo stability of a bioactive compound;
- Studying tissue distribution and accumulation of molecular entities (either single dose or repeated doses) and/or metabolites especially in relation to their potential sites of action;
- Predicting blood-brain barrier penetration;
- Predicting transport properties of chemical compounds in liver, kidney, intestine, and target organs;
- Studying the influence of transporter variants on chemical compound excretion;
- Identifying specific inhibitors and substrates that permit characterization of individual transporters;
- Predicting metabolism, metabolic stability, or metabolic clearance;
- Studying activation or inhibition of enzymes involved in ADME process;
- Evaluating drug-drug or drug-nutrient interactions;
- Quantitating and identifying parent drugs, drug metabolites, and/or degradation products in target organs;

- Predicting general toxicity following single dose and repeated doses, toxicity from acute or chronic exposure to chemical compounds, delayed toxicity, local tolerance, carcinogenicity, genotoxicity, or developmental toxicity;
- Predicting organ toxicity including hepatotoxicity, nephrotoxicity, cardiac toxicity, neurotoxicity, pulmonary toxicity, and reproductive toxicity;
- Evaluating ADME/TOX properties of combination therapies;
- Comparing ADME/TOX properties of synthetic compounds and herbal compounds;
- Predicting drug-induced QT interval prolongation;
- Developing human stem cells to monitor drug toxicities;
- Developing genomics-, proteomics-, or metabolomics-based approaches to identify ADME/TOX properties for use in preclinical testing;
- Identifying novel biomarkers to predict ADME/TOX properties of molecular entities and potential drug interactions;
- Studying age-related genetic and phenotypic changes that affect drug toxicity;
- Evaluating ethnicity-associated ADME/TOX properties;
- Identifying tissue repair and protective mechanisms.

Once validated, these tools or models could be employed in optimizing new lead compounds. These preclinical tools are likely to improve knowledge management and decision-making during drug discovery and development.

Data obtained from new, exploratory approaches must be correlated with those of traditional ADME/TOX studies and available clinical outcome data in order to demonstrate the utility and the major enhancement of a new approach over existing methodology. All funded grantees are encouraged to release preclinical ADME/TOX data generated from supported projects to the research community in a timely manner.

Section II. Award Information

1. Mechanism(s) of Support

This funding opportunity will use the R21 Exploratory/Developmental Research Grants award mechanism. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project. Plans to re-issue this RFA are indefinite. If it is not re-issued, applications that are not funded in the competition may be re-submitted as NEW investigator-initiated applications using the standard receipt dates for New applications described in the instructions to the PHS 398 application.

This funding opportunity uses just-in-time concepts. It also uses the modular budget format described in the PHS 398 application instructions. (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular budget format described in the PHS 398 application instructions.

2. Funds Available

The NIH intends to initially commit approximately $2 million in FY 2005 to fund four to seven new grants in response to this RFA. An applicant may request a project period of up to four years and a budget for direct costs up to $250,000 per year. Indirect costs associated with consortia or subcontracts will not be considered as part of the $250,000 direct cost limit (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-040.html). Requests for equipment must be considered as part of the $250,000 direct cost limit. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of the NIH provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

You may submit (an) application(s) if your organization has any of the following characteristics:

- For-profit organizations
- Non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State government
- Units of local government
- Eligible agencies of the Federal government
- Domestic and foreign institutions/organizations

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

2. Cost Sharing

This program does not require cost sharing as defined in the current NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/nihgps_Part2.htm#matching_or_cost_sharing

3. Other-Special Eligibility Criteria

An applicant may submit only one application as the principal investigator in response to this RFA. An institution or organization may submit more than one application in response to this RFA.

Section IV. Application and Submission Information

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1. Address to Request Application Information

The PHS 398 application instructions are available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a D&B Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at http://www.dnb.com/. The D&B number should be entered on line 11 of the face page of the PHS 398 form.

See also Subsection VI.2. Additional Requirements for additional information.

The title and number of this funding opportunity must be typed on line 2 of the face page of the application form and the YES box must be checked.

3. Submission Dates

3.A. Receipt, Review and Anticipated Start Dates

Letter of Intent Receipt Date: December 17, 2004
Application Receipt Date: January 21, 2005
Peer Review Date: June or July 2005
Council Review Date: September 2005
Earliest Anticipated Start Date: September 10, 2005

3.A.1. Letter of Intent

Prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed research
- Name, address, and telephone number of the Principal Investigator
- Names of other key personnel
- Participating institutions
- Number and title of this funding opportunity

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document.

The letter of intent should be sent to:

Richard Okita, Ph.D.
Division of Pharmacology, Physiology, and Biological Chemistry
National I nstitute of General Medical Sciences
45 Center Drive, Room 2AS-49A, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-1826
FAX: 301-480-2802
Email: okitar@nigms.nih.gov

3.B. Sending an Application to the NIH

Applications must be prepared using the PHS 398 research grant application instructions and forms as described above. Submit a signed, typewritten original of the application, including the checklist, and three signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

At the time of submission, two additional copies of the application and all copies of the appendix material must be sent to:

Helen R, Sunshine, Ph.D.
Office of Scientific Review National Institutes of General Medical Sciences, NIH
45 Center Drive, Room 3AN.12F, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-2881
FAX: (301) 480-8506
Email: sunshineh@nigms.nih.gov

Using the RFA Label: The RFA label available in the PHS 398 application instructions must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/label-bk.pdf.

3.C. Application Processing

Applications must be received **on or before the application receipt date** listed in the heading of this funding opportunity. If an application is received after that date, it will be returned to the applicant without review. Upon receipt, applications will be reviewed for completeness by CSR and responsiveness by NIGMS. Incomplete and nonresponsive applications will not be reviewed and will be returned.

The NIH will not accept any application in response to this funding opportunity that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to a funding opportunity, it is to be

prepared as a NEW application. That is, the application for the funding opportunity must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within eight (8) weeks.

4. Intergovernmental Review

This initiative is not subject to intergovernmental review .

5. Funding Restrictions

All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm. (See also Section VI.3. Award Criteria.)

6. Other Submission Requirements

SUPPLEMENTARY INSTRUCTIONS: The R21 mechanism is intended to encourage new exploratory and developmental research projects. The projects may involve considerable risk but lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models or applications that could have major impact on a field of biomedical, behavioral, or clinical research. Exploratory/developmental grant support is for new projects only; competing continuation applications will not be accepted. For example, long-term projects or projects designed to increase knowledge in a well-established area will not be considered for R21 awards. The proposed studies should break new ground or extend previous discoveries toward new directions or applications.

Use the PHS 398 form with the following modifications: Follow instructions for preparing a R21 application at http://grants.nih.gov/grants/guide/pa-files/PA-03-107.html. Items a - d of the Research Plan (Specific Aims, Background and Significance, Preliminary Studies, and Research Design and Methods) may not exceed a total of 15 pages. No preliminary data are required but may be included if they are available. Items e ? g (human subjects/vertebrate animals/literature cited) do not count against the page limit.

Specific Instructions for Modular Grant applications.

Applications requesting up to $250,000 per year in direct costs must be submitted in a modular budget format. The modular budget format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular budgets. Additional information on modular budgets is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

Plan for Sharing Research Data

All applicants must include a plan for sharing research data in their application. The data sharing policy is available at http://grants.nih.gov/grants/policy/data_sharing. All investigators responding to this funding opportunity should include a description of how final research data will be shared, or explain why data sharing is not possible.

The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score.

Sharing Research Resources

NIH policy requires that grant award recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication. NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part7.htm#_Toc54600131. Investigators responding to this funding opportunity should include a plan for sharing research resources addressing how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the data sharing plan and the resources sharing plan will be considered by Program staff of the funding

organization when making recommendations about funding applications. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report. (PHS 2590). See Section VI.3. Award Criteria.

Section V. Application Review Information

1. Criteria

This program does not require cost sharing as defined in the current NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/nihgps_Part2.htm#matching_or_cost_sharing.

2. Review and Selection Process

Applications submitted for this funding opportunity will be assigned to the ICs on the basis of established PHS referral guidelines.

Appropriate scientific review groups convened in accordance with the standard NIH peer review procedures (http://www.csr.nih.gov/refrev.htm) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score.
- Receive a written critique.
- Receive a second level of review by the National Advisory General Medical Sciences (NAGMS) Council.

3. Merit Review Criteria

The goals of NIH's supported research are to advance our understanding of biological systems, to improve the control of disease, and to enhance health. In their written critiques, reviewers will be asked to comment on each of the following criteria in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

2. Approach. Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

4. Investigators. Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project (if applicable)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

3.A. Additional Review Criteria:

In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

Protection of Human Subjects from Research Risk: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Inclusion of Women, Minorities and Children in Research: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Care and Use of Vertebrate Animals in Research: If vertebrate animals are to be used in the project, the five items described under Section F of the PHS Form 398 research grant application instructions will be assessed.

3.B. Additional Review Considerations

Budget: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. The priority score should not be affected by the evaluation of the budget.

3.C. Sharing Research Data

Data Sharing Plan: The reasonableness of the data sharing plan or the rationale for not sharing research data **will** be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score. The funding organization will be responsible for monitoring the data sharing policy. http://grants.nih.gov/grants/policy/data_sharing.

3.D. Sharing Research Resources

NIH policy requires that grant award recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication. NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps and http://ott.od.nih.gov/newpages/rtguide_final.html. Investigators responding to this funding opportunity should include a sharing research resources plan addressing how unique research resources will be shared or explain why sharing is not possible. Reviewers will assess whether applicants have addressed intellectual property issues in their applications in order to prevent interference with the progress of research and sharing of information with the research community.

The adequacy of the resources sharing plan will be considered by Program staff of the funding organization when making recommendations about funding applications. Program staff may negotiate modifications of the data and resource sharing plans with the Principal Investigator before recommending funding of an application. The final version of the data and resource sharing plans negotiated by both will become a condition of the award of the grant. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590). See Section VI.3. Award Criteria.

Section VI. Award Administration Information

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1. Award Notices

After the peer review of the application is completed, the Principal Investigator will also receive a written critique called a summary statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm

For each application that is approved for funding, a formal notification in the form of a notice of award will be provided to the applicant organization. The notice of award signed by the grants management officer is the authorizing document.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NGA (Notice of Grant Award) are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

2. Administrative Requirements

Program staff will negotiate modifications of the data and resource sharing and intellectual property plans with the Principal Investigator before recommending funding of an application. The final version of the data and resource sharing plans negotiated by both will become a condition of the award of the grant. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590).

All NIH Grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm.

3. Award Criteria

The following will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review
- Availability of funds
- Relevance of program priorities

4. Reporting

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 2590 annually: http://grants.nih.gov/grants/funding/2590/2590.htm and financial statements as required in the NIH Grants Policy Statement.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific/Research Contacts:

Richard Okita, Ph.D.
Division of Pharmacology, Physiology, and Biological Chemistry
National Institute of General Medical Sciences
45 Center Drive , Room 2AS-49A, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-1826
FAX: 301-480-2802
Email: okitar@nigms.nih.gov

Min H. Song, Ph.D.
Division of Cancer Treatment and Diagnosis
National Cancer Institute
6130 Executive Blvd., Room 8153, MSC-7456
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 496-8783
Fax: (301) 402-5200
Email: songm@mail.nih.gov

2. Peer Review Contacts:

Helen R. Sunshine, Ph.D.
Office of Scientific Review National Institutes of General Medical Sciences, NIH
45 Center Drive, Room 3AN.12F, MSC 6200
Bethesda , MD 20892-6200

Telephone: (301) 594-2881
FAX: (301) 480-8506
Email: sunshineh@nigms.nih.gov

3. Financial or Grants Management Contacts:

Antoinette Holland
Grants Administration Branch
National Institute of General Medical Sciences
45 Center Drive Room 2AN.50B, MSC 6200
Bethesda , MD 20892-6200
Telephone: (301) 594-5132
FAX: (301) 480-2554
Email: hollanda@nigms.nih.gov

Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:
Recipients of PHS support for activated involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf), as mandated by the Health Research Extension Act of 1985 (http://grants.nih.gov/grants/olaw/references/hrea1985.htm), and the USDA Animal Welfare Regulations (http://www.nal.usda.gov/awic/legislat/usdaleg1.htm), as applicable.

Human Subjects Protection:
Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

Data and Safety Monitoring Plan:
Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity, and dose-finding studies (phase I); efficacy studies (Phase II); efficacy, effectiveness and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants. (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

Sharing Research Data:
Investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible. http://grants.nih.gov/grants/policy/data_sharing

Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, State and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Sharing of Model Organisms:
NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html). At the same time the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh Dole Act (see the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal beginning with the October 1, 2004 receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Inclusion of Women And Minorities in Clinical Research:
It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is

inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:
The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm.

Required Education on The Protection of Human Subject Participants:
NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

Human Embryonic Stem Cells (hESC):
Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html . Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see http://escr.nih.gov/) It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s)to be used in the proposed research. Applications that do not provide this information will be returned without review.

Public Access to Research Data through the Freedom of Information Act:
The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Standards for Privacy of Individually Identifiable Health Information:
The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule", on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs in NIH Grant Applications or Appendices:
All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

Authority and Regulations:
This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Department of Health and Human Services

National Institutes of Health (NIH)
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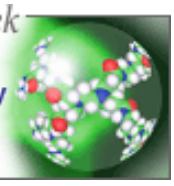

NCI's Nanotechnology Web Site

Medical Investigation on TV: Facts about

- Anthrax
- Biodefense Research

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Department of Health and Human Services

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Weekly NIH Funding Opportunities and Notices

NIH Guide for Grants and Contracts

October 29, 2004

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  (RFA-DC-05-001)
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  National Institute of Child Health and Human Development
  Application Receipt Date(s): February 24, 2005

- Site Specific Approaches to Prevention or Management of Pediatric Obesity
  (RFA-DK-04-013)
  National Institute of Diabetes and Digestive and Kidney Diseases
  National Cancer Institute
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  Application Receipt Date(s): January 24, 2005

- Specialized Cooperative Centers Program in Reproduction Research
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- The Centers for Education and Research on Therapeutics (CERTs)
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- Research on the Economics of Diet, Activity, and Energy Balance
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- Cooperative Drug Development Group (CDDG) for the Treatment of Mental Illness
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